| L Number | Hits | Search Text | DB | Time stamp |
|---|---|---|---|---|
| 3 | 1 | ("20020099526").PN. | USPAT; US-PGPUB | 2003/03/05 15:07 |
| 6 | 4 | topomeric adj3 (alignment or allignment) | USPAT; US-PGPUB | 2003/03/05 15:11 |
| 9 | 4 | topomeric and (alignment or allignment) | USPAT; US-PGPUB | 2003/03/05 15:11 |
| 12 | 4 | topomeric adj3 rules | USPAT; US-PGPUB | 2003/03/05 15:11 |
| 15 | 2 | topomeric and (rule or rules or alignment or allignment) | EPO; JPO; DERWENT; IBM_TDB | 2003/03/05 15:18 |
| 20 | 1 | 1997-393887.NRAN. | DERWENT | 2003/03/05 15:12 |
| 21 | 6 | topomeric | USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB | 2003/03/05 15:18 |

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FILE 'HOME' ENTERED AT 15:21:50 ON 05 MAR 2003

=> index bioscience

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                                                            0.21        0.21

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       BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT,
       CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE,
       DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 15:22:13 ON 05 MAR 2003

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L1   QUE TOPOMERIC AND (ALIGNMENT OR ALLIGNMENT OR RULE)

=> s topomeric

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           1   FILE BIOSIS
           1   FILE BIOTECHNO
           1   FILE CANCERLIT
           6   FILE CAPLUS
           1   FILE EMBASE
           4   FILE IFIPAT
           1   FILE MEDLINE
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  51 FILES SEARCHED...
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           3   FILE SCISEARCH
           4   FILE USPATFULL
           2   FILE WPIDS
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L2   QUE TOPOMERIC

=> d rank

F1            6   CAPLUS
F2            4   IFIPAT
F3            4   USPATFULL
F4            3   SCISEARCH
F5            2   WPIDS
F6            2   WPINDEX
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| F7 | 1 | BIOBUSINESS |
| F8 | 1 | BIOSIS |
| F9 | 1 | BIOTECHNO |
| F10 | 1 | CANCERLIT |
| F11 | 1 | EMBASE |
| F12 | 1 | MEDLINE |
| F13 | 1 | PASCAL |
| F14 | 1 | PROMT |

=> file f1 f4 f7-f14; s l2; dup rem l3

| | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| COST IN U.S. DOLLARS | 1.65 | 1.86 |

FULL ESTIMATED COST

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L3 17 L2

PROCESSING COMPLETED FOR L3
L4 9 DUP REM L3 (8 DUPLICATES REMOVED)

=> d bib ab 1-9

L4 ANSWER 1 OF 9 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 2002:699268 SCISEARCH
GA The Genuine Article (R) Number: 583RL
TI Virtual screening with **topomeric** CoMFA.
AU Cramer R D
CS Tripos, St Louis, MO 63144 USA
CYA USA



by: Mary K. Zeman

ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, (AUG 2002) Vol. 224, Part 1, pp. U477 77. MA 056-COMP.
Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA.
ISSN: 0065-7727.
DT Conference; Journal
LA English
REC Reference Count: 0

L4 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 2002:615734 CAPLUS
TI Virtual screening with **topomeric** CoMFA
AU Cramer, Richard D.
CS Tripos, St. Louis, MO, 63144, USA
SO Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), COMP-056 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69CZPZ
DT Conference; Meeting Abstract
LA English
AB Topomerically aligning the fragments of the input structures has proven to be a remarkably robust starting point for automated CoMFA studies. Acceptable results were obtained in repeating all 15 of 15 published studies, with overall av. q2 and errors of "true prediction" indistinguishable from the literature summary results. The resulting CoMFA models are perfectly suited for searching the vast ChemSpace database (>1013 synthetically accessible drug-like structures), while targeting improved activity as well as similarity, at negligible performance cost. Thus a general "high-throughput-design" methodol. exists, capable of shortening high quality information-based complete design-test-synthesis cycles to weeks, in the real world.

L4 ANSWER 3 OF 9 PROMT COPYRIGHT 2003 Gale Group

AN 1998:182842 PROMT
TI Tripos Inc. Announces New Compound Library Suite and Construction of New High Throughput Research Facility
SO PR Newswire, (16 Apr 1998) pp. 0416CGTH018.
LA English
WC 541
*FULL TEXT IS AVAILABLE IN THE ALL FORMAT*
AB ST. LOUIS, April 16 /PRNewswire/ -- Today Tripos, Inc. (Nasdaq: TRPS) announced the availability of a new chemical library product from its Accelerated Discovery Services (ADS) group. This product is a general lead-finding screening library composed of individual compounds of defined, high purity which meet Tripos' design criteria for maximum diversity as defined by **topomeric** and fingerprint descriptors.
The initial library offering consists of approximately 30,000 compounds which will be available for shipment by the end of June 1998.
Tripos will aggressively augment this library and it is anticipated that it will grow to over 60,000 compounds by the end of 1998. All new compounds added to the library will meet the stipulated criteria for purity and diversity. The library offering will be available in custom formats and platings, and will come with an electronic database ready for registration at the customer site.
"The compound library market continues to support substantial growth and those who can respond rapidly and flexibly to meet customer requirements will reap the benefits. Tripos will address the market demand for an easy selection process, high purity, rapid availability, and diversity of general screening compounds. Tripos will also provide pre-defined pure libraries designed for particular families of biological targets as standard products. Finally, Tripos will be able to address specific research needs of our customers in lead follow-up and refinement through collaborative research agreements. This unprecedented product range and flexibility will drive the growth of ADS," stated Martin Stuart, Vice President of Accelerated Discovery Products at Tripos.
Simultaneously, Tripos announced the initiation of construction of a

multi-million dollar [redacted]te-of-the-art chemical research [redacted]nd production facility at Tripos Re[redacted]tor Research (TRR) in Bude, Eng[redacted]nd. Tripos is rapidly expanding the capabilities of this recently acquired subsidiary to accommodate the demand for novel, highly characterized chemical compounds both for general screening libraries and for focused libraries and lead refinement through to traditional medicinal chemistry. This activity is key to Tripos' goal to become a key partner to our customers in their research and development activities.
THIS IS AN EXCERPT: COPYRIGHT 1998 PR Newswire Association, Inc.

L4 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 1998:442463 CAPLUS
DN 129:77998
TI Bioisosterism and molecular diversity
AU Clark, Robert D.; Ferguson, Allan M.; Cramer, Richard D.
CS Tripos, Inc., St. Louis, MO, 63144, USA
SO Perspectives in Drug Discovery and Design (1998), 9/10/11(3D QSAR in Drug Design: Ligand/Protein Interactions and Molecular Similarity), 213-224
CODEN: PDDDEC; ISSN: 0928-2866
PB Kluwer Academic Publishers
DT Journal; General Review
LA English
AB A review with 27 refs. is given on bioisosterism and mol. diversity including theor. considerations, **topomeric** comparative mol. field anal. (CoMFA), inertial field orientation (IFO-CoMFA), and validation.

L4 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
AN 1996:422682 CAPLUS
DN 125:75368
TI Bioisosterism as a Molecular Diversity Descriptor: Steric Fields of Single "**Topomeric**" Conformers
AU Cramer, Richard D.; Clark, Robert D.; Patterson, David E.; Ferguson, Allan M.
CS Tripos Inc., St. Louis, MO, 63144, USA
SO Journal of Medicinal Chemistry (1996), 39(16), 3060-3069
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The comparative mol. field anal. steric field of a single "**topomeric**" conformer is introduced as a mol. diversity descriptor particularly useful for combinatorial chem. involving variations around a fixed "core". Using this new descriptor, 736 com. available thiols are divided into 231 bioisosteric clusters, whose compns. agree at least as well with medicinal chem. experience and intuition as do clusters derived from Tanimoto differences between 2D fragment occurrences. However, in practice **topomeric** steric fields complement 2D fingerprints, being the two most frequently useful descriptors yet found for neighborhood-based design of combinatorial libraries.

L4 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 1994:144701 CAPLUS
DN 120:144701
TI Three equivalent gradient lines for the inversion path of PF3 molecule
AU Minyaev, R. M.
CS Nauchno-Issled. Inst. Fiz. Org. Khim., Rostav-on Don, Russia
SO Zhurnal Fizicheskoi Khimii (1993), 67(11), 2205-9
CODEN: ZFKHA9; ISSN: 0044-4537
DT Journal
LA Russian
AB All crit. points with rank .ltoreq. 3 on the potential energy surface in the region between the two min. corresponding to the pyramidal (C3v) structure of the PF3 mol. were calcd. were calcd. using the Hartree-Fock method with the STO6-31G* basis. The reaction path for the pyramidal inversion in PF3 consists of three equiv. (phys. indistinguishable)

gradient lines, passi[redacted]through three **topomeric** T-shap[redacted] transition structures[redacted]. e. the inversion reaction pr[redacted]eds simultaneously along three lines (channels that connect the two min.). This appears to be the first example of a chem. reaction that proceeds simultaneously along three reaction channels that start in one min. and end in another neighboring min.

L4 ANSWER 7 OF 9 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 91:179895 SCISEARCH
GA The Genuine Article (R) Number: FC319
TI MOLECULAR AND CRYSTAL-STRUCTURE OF ORTHO-TELLURATED AZOMETHINES WITH INTRAMOLECULAR N-]TE COORDINATION
AU MINKIN V I (Reprint); SADEKOV I D; MAKSIMENKO A A; KOMPAN O E; STRUCHKOV Y T
CS ROSTOV DON STATE UNIV, INST PHYS & ORGAN CHEM, ROSTOV, USSR (Reprint); AN NESMEYANOV ORGANOELEMENT CPDS INST, MOSCOW, USSR
CYA USSR
SO JOURNAL OF ORGANOMETALLIC CHEMISTRY, (1991) Vol. 402, No. 3, pp. 331-348.
DT Article; Journal
FS PHYS
LA ENGLISH
REC Reference Count: 50
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB Novel reactions have been discovered and studied of C(aliph.)-Te bond scission in omicron-butyltellurobenzalanilines under the action of halogens, which afford 2-halogenotellurenyl- and 2-trihalogenotellurobenzalanilines in high yields. The series of azomethines have been synthesized with different tellurium-containing groups in omicron-positions with respect to the C = N bond. The effects of structural factors upon the length of N --> Te intramolecular coordination bonds have been studied by the following methods: X-ray structural determinations, dipole moments, H-1 and Te-125 NMR spectroscopy and IR spectroscopy. In Te(II) derivatives, the shortest intramolecular N --> Te contact (2.23-angstrom) is formed in 2-chlorotellurenyl derivatives XIIIb. Bis(2-formylphenyl)tellurium imines XIVa exist in the crystal form as 10-Te-3 telluranes, in which long intramolecular fractional N --> Te bonds (2.70-2.72-angstrom) have been detected, with the basicity of the imine N atom no practical effect on their length. The Te-125 NMR spectrum of the N-15 labelled bis[2-(phenyl)iminomethinylphenyl]telluride shows that in solutions of this compound a very fast (on an NMR timescale), Te-N and Te <-- N bond scrambling occurs owing to a dynamic equilibrium between the **topomeric** 10-Te-3 structures that apparently takes place via the 12-Te-4 tellurane intermediates. The intramolecular coordination bond in the Te(IV) derivative, (2-phenyliminomethinylphenyl)butylmethyl telluronium perchlorate, belongs to the longest Te --> N bonds (2.75-angstrom). For the first time, the Te-125-N-15 spin-spin coupling constants are reported for a number omicron-tellurated azomethines.

L4 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 1977:468057 CAPLUS
DN 87:68057
TI Synthesis and acylation of pyrrolinones
AU Moon, Malcolm W.
CS Upjohn Co., Kalamazoo, MI, USA
SO Journal of Organic Chemistry (1977), 42(13), 2219-23
CODEN: JOCEAH; ISSN: 0022-3263
DT Journal
LA English
AB Et-5-acetyl-2,4-dimethylpyrrole-3-carboxylate (I; R = EtO, R1 = Me) reacted with concd. HNO3 to give pyrrolinone II (R, R1 = same) and nitropyrrole III (R = EtO). I (R = OMe, R1 = Me, OMe, OEt, NMe2, NMeEt, NEt2; R = Me, R1 = EtO; R = R1 = OEt) were also oxidized to pyrrolinones II. Di-Et 2-acetyl-3-methylsuccinate reacted with NH3 to give a mixt. of Et 4,5-dihydro-2,4-dimethyl-5-oxo-1H-pyrrole-3-carboxylate (IV) and its .DELTA.3 isomer. Acylation of IV and its N-methyl analog with various reagents was studied. The reaction products were formulated as

pyrrolinones or 5-acy[redacted]ypyrroles on the basis of thei[redacted]pectral (1H and 13C NMR, UV and IR) p[redacted]erties.

L4 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 1975:513517 CAPLUS
DN 83:113517
TI Apicophilicity of the benzoyl group in five-coordinate phosphoranes
AU Trippett, Stuart; Whittle, Peter J.
CS Dep. Chem., Univ. Leicester, Leicester, UK
SO Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1975), (13), 1220-2
CODEN: JCPRB4; ISSN: 0300-922X
DT Journal
LA English
AB The pseudo rotation of the spirophosphorane I (R = Bz) between 2 **topomeric** trigonal bypyramids occurred via an intermediate with an apical Bz group and a disequational 5-membered ring. The potential barrier to pseudorotation to the apical Bz conformation was detd. as 20.9 kcal/mole from NMR. Comparison with I (R = H) which has a lower potential barrier, indicated that the Bz group has a similar apicophilicity to the PhO or PhS groups. 1H and 19F NMR of the phosphorane II, prepd. from BzPMe2 and XeF2, indicated restricted rotation about the Bz-P bond with a barrier to rotation <8 kcal/mole.

US-PAT-NO: 6185506
DOCUMENT-IDENTIFIER: US 6185506 B1

TITLE: Method for selecting an optimally diverse library of small molecules based on validated molecular structural descriptors

DATE-ISSUED: February 6, 2001


INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Cramer; Richard D. | O'Fallon | MO | N/A | N/A |
| Patterson; David E. | St. Louis | MO | N/A | N/A |
| Clark; Robert D. | St. Louis | MO | N/A | N/A |
| Ferguson; Allan M. | St. Louis | MO | N/A | N/A |


US-CL-CURRENT: 702/19; 435/DIG.51 ; 702/22 ; 702/30


ABSTRACT:

The use of biological screening purposes of a subset (library) of a large combinatorially accessible chemical universe increases the efficiency of the screening process only if the subset contains members representative of the total diversity of the universe. In order to insure inclusion in the subset of molecules representing the total diversity of the universe under consideration, valid molecular descriptors which quantitatively reflect the diversity of the molecules in the universe are required. A unique validation method is used to examine both a new three dimensional steric metric and some prior art metrics. With this method, the relative usefulness/validity of individual metrics can be ascertained from their application to randomly selected literature data sets. By the appropriate application of validated metrics, the method of this invention selects a subset of a combinatorial accessible chemical universe such that the molecules of the subset are representative of all the diversity present in the universe and yet do not contain multiple members which represent the same diversity (oversample). The use of the neighborhood definition of a validated metric may also be used to combine (without oversampling the same diversity) any number of combinatorial screening libraries.


58 Claims, 43 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 27

---------- KWIC ---------

Brief Summary Text - BSTX:

It is a further object of this invention to define a process to derive CoMFA steric fields (and, if desired, additional relevant fields) using topomeric alignment so that the resulting descriptor is valid.

Brief Summary Text - BSTX:

It is a further object of this invention to teach that topomeric alignments may be used to describe molecular conformations.

Drawing Description Text - DRTX:

FIGS. 6A through 6C show three molecular structures numbered and marked in accordance with the topomeric alignment rule.

Detailed Description Text - DETX:

A. Topomeric Alignment

Detailed Description Text - DETX:

TOPOMERIC ALIGNMENT shall mean conformer alignment based on a set of alignment rules.

Detailed Description Text - DETX:

It has been discovered that a CoMFA approach to generating a molecular structural descriptor using a specially developed alignment procedure,

topomeric alignment, produces a three dimensional descriptor of molecules which is shown to be valid by the method outlined above. In addition, this new descriptor provides a powerful tool with which to design combinatorial screening libraries. It is equally useful any time selection based on diversity from within a congeneric series is required. A full description of CoMFA and the generation of molecular interaction energies is contained in U.S. Pat. Nos. 5,025,388 and 5,307,287. The disclosures of these patents are incorporated in this Application. The usual challenge in applying CoMFA to a known set of molecules is to determine the proper alignment of the molecular structures with respect to each other. Two molecules of identical structure will have substantially different molecular interaction energies if they are translated or rotated so as to move their atoms more than about 4 .ANG. from their original positions. Thus, alignment is hard enough when applying CoMFA to analyze a set of molecules which interact with the same biological receptor. The more difficult question is how to "align" molecules distributed in multidimensional chemistry space to create a meaningful descriptor with respect to arbitrary and unknown receptors against which the molecules will ultimately be tested. The topomeric alignment procedure was developed to correct the usual CoMFA alignments which often over-emphasize a search for "receptor-bound", "minimum energy", or "field-fit" conformations. It has been discovered that, when congenericity exists, a meaningful alignment results from overlaying the atoms that lie within some selected common substructure and arranging the other atoms according to a unique canonical rule with any resulting steric collisions ignored. When CoMFA fields are generated for molecules so aligned, it has been discovered that the resulting field differences are a valid molecular structural descriptor.

Detailed Description Text - DETX:

A. Topomeric Alignment

Detailed Description Text - DETX:

Usually a CoMFA modeler seeks low energy conformations. However, if alignment with unknown receptors is desired (such as is the case in designing combinatorial screening libraries for general purpose screening), then the major goal in conformer generation must be that molecules having similar topologies should produce similar fields. In fact, topomeric CoMFA fields may be used as a validated diversity descriptor to identify molecules with similar or dissimilar structures anytime there is a problem of having more compounds than can be easily dealt with. Thus, its applicability extends well beyond its

use in combinatorial chemistry to all situations where it is necessary to analyze an existing group of compounds or specify the creation of new ones. The topomeric alignment procedure is especially applicable to the design of a combinatorial screening library. Typically, as noted earlier, in the creation of combinatorially derived compounds there is often an invariant central core to which a variety of side chains (contributed by reactants of a particular class) are attached at the open valences. Within the combinatorial products, this central core tethers each of the side chains contributed by any set of reactants into the same relative position in space. In the language of CoMFA alignments, the side chains contributed by each reactant can thus be oriented by overlapping the bond that attaches the side chain to the central core and using a topomeric protocol to select a representative conformation of the side chain. Nowhere does the prior art suggest that a topomeric protocol could possibly yield a meaningful alignment. Indeed, the prior art inherently teaches away from the idea because the topomerically derived conformers often may be energetically inaccessible and incapable of binding to any receptor.

Detailed Description Text - DETX:

The following topologically-based rules will generate a single, consistent, unambiguous, aligned topomeric conformation for any molecule lacking chiral atoms. The software necessary to implement this procedure is contained in Appendix "A". The starting point for a topomeric alignment of a molecule is a CONCORD generated three dimensional model which is then FIT as a rigid body onto a template 3D model by least-squares minimization of the distances between structurally corresponding atoms. By convention, the template model is originally oriented so that one of its atoms is at the Cartesian origin, a second lies along the X axis, and a third lies in the XY plane.

Detailed Description Text - DETX:

As for the dihedral angle values themselves, torsion 4-5-8-9 is set to 60 degrees, because both the 4-5 and 8-9 bonds are within a ring; torsions 9-10-14-15 and attached -1-3-4 become 90.degree., because only the 3-4 and 9-10 bonds respectively are cyclic; and the attached -1-2-16 dihedral becomes 180.degree. since none of the bonds are cyclic. It should be noted that this topomeric alignment procedure will not work with molecules containing chiral centers since, for each chiral center, two possible three dimensional configurations are possible for the same molecule, and, clearly, each configuration by the above rules would yield a different topomeric conformer.

Detailed Description Text - DETX:

The preferred method for selecting reactants based on diversity is shown schematically at the third filter in FIG. 11. A diversity selection based on three dimensional steric measures begins by: 1) generating 3D structures for the reactants; 2) aligning the 3D molecular structures according to the topomeric alignment rules; 3) generating CoMFA steric field values for the reactants including, if desired, hydrogen bonding field, and applying a rotatable bond attenuation factor; and 4) calculating pairwise topomeric CoMFA differences for every pair of reactants. At this point the steric diversity of the reactant space has been mapped into the topomeric CoMFA metric space. From the validation of the topomeric CoMFA metric, it was found that the neighborhood radius for an apparent activity difference of 2 log units was defined by a distance of approximately 80-100 topomeric CoMFA units (kcal/mole). Therefore, at this point, the method of the invention clusters (using hierarchical clustering) the reactants in topomeric CoMFA space so that reactants having a pairwise difference of less than approximately 80-100 units are assigned to the same cluster. Put another way, clustering is continued until the inter-cluster separation is greater than approximately 80-100 units. (If desired, there is some leeway in choosing the exact neighborhood radius in and about the neighborhood range to use for any given biological system. An experienced practioner of the clustering art will easily be able to determine, by noting the natural breaks in the clustering, where about the 80-100 range best clustering is obtained.) This process will produce clusters having reactants whose product activities will only rarely differ by more than approximately 2 log units. If reactant clusters having products activities differing by a greater or lesser amount are desired, the neighborhood distance used may be increased or decreased accordingly. The effect on the neighborhood distance of choosing such other activity range can be seen by viewing the Patterson validating plots for the topomeric CoMFA descriptor.

L4 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
AN 1996:422682 CAPLUS
DN 125:75368
TI Bioisosterism as a Molecular Diversity Descriptor: Steric Fields of Single "**Topomeric**" Conformers
AU Cramer, Richard D.; Clark, Robert D.; Patterson, David E.; Ferguson, Allan M.
CS Tripos Inc., St. Louis, MO, 63144, USA
SO Journal of Medicinal Chemistry (1996), 39(16), 3060-3069
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The comparative mol. field anal. steric field of a single "**topomeric**" conformer is introduced as a mol. diversity descriptor particularly useful for combinatorial chem. involving variations around a fixed "core". Using this new descriptor, 736 com. available thiols are divided into 231 bioisosteric clusters, whose compns. agree at least as well with medicinal chem. experience and intuition as do clusters derived from Tanimoto differences between 2D fragment occurrences. However, in practice **topomeric** steric fields complement 2D fingerprints, being the two most frequently useful descriptors yet found for neighborhood-based design of combinatorial libraries.